Remarks

Applicants appreciate the withdrawal of the rejection of claims 32, 56-58, and 60 under 35 U.S.C. § 112, second paragraph.

The Invention

Claims 28-32 and 51-60 are directed to a composition comprising a cell having a molecular complex bound to its surface. The molecular complex comprises at least four fusion proteins. Two of the fusion proteins comprise an immunoglobulin heavy chain (including the variable region) and an extracellular portion of a first transmembrane polypeptide. The other two fusion proteins comprise an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide. These fusion proteins associate to form a molecular complex that comprises two ligand binding sites. Each ligand binding site is formed by the extracellular domains of the first and second transmembrane polypeptides. The affinity of the molecular complex for a cognate ligand is increased at least two-fold over a dimeric molecular complex that consists only of a first and a second fusion protein.

A clean copy of the entire claim set, incorporating the amendments made to claims 56 and 57, is provided in Appendix 2.

The Rejection of Claims 56 and 57 Under 35 U.S.C. § 112, second paragraph

Claims 56 and 57 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse the rejection.

The Final Office Action maintains that the terms "passively bound" and "actively bound" in claims 56 and 57, respectively, are unclear. To advance prosecution, claims 56 and 57 have

been amended to delete these recitations. Amended claim 56 now recites the step by which passive binding is accomplished. This amendment is supported in the specification in the paragraph bridging pages 28 and 29, which describes a method of passive binding. Amended claim 57 now recites the steps by which active binding is accomplished. This amendment is supported by FIG. 3 and at page 19, lines 10-13, where the method of active binding is described.

Amended claims 56 and 57 are clear and definite. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 28-32 and 51-60 Under 35 U.S.C. § 112, first paragraph

Claims 28-32 and 51-60 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse the rejection.

As an initial matter, Applicants respectfully point out that the Final Office Action has misstated the scope of claims 28-32 and 51-60. The Final Office Action asserts that "the composition of the instant invention utilizes a peptide linker." This statement is incorrect. The claims are directed to a composition comprising a cell to which a molecular complex composed of at least four fusion proteins is bound. The claims do not recite use of a peptide linker to bind the recited molecular complex to the cell surface.

The Final Office Action has not made a *prima facie* case that claims 28-32 and 51-60 as properly interpreted are not enabled. The recited molecular complex that is bound to the cell surface is composed of at least four fusion proteins. The association of the recited fusion proteins forms two ligand binding sites. The specification teaches that molecular complexes in which the ligand binding sites are occupied also can be bound to a cell surface:

> Molecular complexes of the invention can be bound to the surface of a cell, such as a dendritic cell. A population of molecular complexes in which all ligand binding sites are bound to identical antigenic peptides can also be bound to the cell.

Page 22, lines 29. The Final Office Action doubts this statement and speculates that use of a peptide linker to bind the recited molecular complexes to the cell surface would affect the function of the fusion proteins of the molecular complex. Paragraph bridging pages 3 and 4. Based on this speculation, the Final Office Action concludes that claims 28-32 and 51-60 are not enabled. To support the rejection, the Final Office Action cites Burgess *et al.*, *J. Cell. Biol. 111*, 2129-38, 1990 ("Burgess") as teaching that proteins are sensitive to alterations of even a single amino acid. Page 3, lines 17-21. The Final Office Action also faults the specification for not providing a working example of a molecular complex that is bound to a cell surface by means of a peptide linker.

Neither the lack of a working example nor the citation of Burgess is sufficient to support a *prima facie* case that claims 28-32 and 51-60 are not enabled. First, working examples are not required to enable an invention. *In re Long*, 368 F.2d 892, 895, 151 U.S.P.Q. (BNA) 640, 642 (C.C.P.A. 1966). Those of skill in the art knew how to bind proteins to cell surfaces long before this specification was filed, and the Final Office Action concedes that "methods of linking a protein or molecule to the surface of a cell are well known and are possible." Page 3, lines 13-15. In view of this knowledge in the art, the lack of a working example should not be given undue weight.

Second, to support a finding of non-enablement, the Office must not only explain why it doubts that molecular complexes bound to the cell surface via a peptide linker would function as described (*i.e.*, would bind ligands at their ligand binding sites), but also must support its doubt

"with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. (BNA) 367, 370 (C.C.P.A. 1971). The rejection does not meet this standard. The Final Office Action only speculates that a peptide linker would affect the function of the molecular complex: "However, the composition of the instant invention utilizes a peptide linker, ***which may or may not effect [sic] the functionality of the molecular complex***." Page 3, lines 15-17, emphasis added. Speculation is not "acceptable evidence or reasoning" that meets the standard of *Marzocchi*.

The Final Office Action cites Burgess as teaching "[t]he sensitivity of [biological function of] proteins to alterations of even a single amino acid in a sequence." Page 3, lines 17-18. The teachings of Burgess, however, bear no relation to whether a peptide linker would affect the function of the recited molecular complex. First, Burgess studied an entirely different protein, HBGF-1. Second, Burgess teaches that alteration of a critical amino acid affects the function of that protein. Burgess teaches that replacement of the lysine residue at position 132 of human heparin binding growth factor 1 (HBGF-1) with glutamic acid reduces the apparent affinity of the growth factor for immobilized heparin, which reduces the biological function of the growth factor. Abstract. Previous studies of HBGF-1 established "a crucial role for lysine 132 in several of the known functions of HBGF-1." Page 2130, second full paragraph. Because a critical amino acid was intentionally altered in the experiments reported in Burgess, it is not surprising that some affect on biological function was observed. Burgess contains no teachings whatsoever relevant to the recited fusion proteins or the use of a protein linker to bind the recited molecular complex to the cell surface.

The U.S. Patent and Trademark Office must support an enablement rejection with acceptable reasoning that is inconsistent with the enabling teachings of the specification.

Marzocchi, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370. Burgess does not provide evidence that is inconsistent with the specification's teaching that the recited molecular complexes can both bind ligands and be bound to a cell surface. The Office has cited no other evidence that is inconsistent with this teaching. Nor has the Office supported the rejection with acceptable reasoning. The Office has merely speculated that a molecular complex anchored to the recited cell surface "may not work" as described. Speculation does not meet the standard of acceptable reasoning that is inconsistent with the enabling teachings of the specification.

The Final Office Action has not made a *prima facie* case of non-enablement. Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

January 2, 2003
Date

By: Lisa M. Hemmendinger
Lisa M. Hemmendinger
Reg. No. 42,653

BANNER & WITCOFF, LTD.
1001 G Street, N.W. – Eleventh Floor
Washington, D.C. 20001-4597
Telephone: 202/508-9100

Appendix 1. Version of the Amended Claims with Markings to Show Changes Made

56. (amended) The composition of claim 32 wherein the antigenic peptides are [passively] bound to the ligand binding sites by a method comprising the step of:

incubating the cell in the presence of the antigenic peptides, whereby the antigenic peptides are bound to the ligand binding sites.

57. (amended) The composition of claim 32 wherein the antigenic peptides are [actively] bound to the ligand binding sites by a method comprising the steps of:

(a) alkaline stripping of the molecular complex to provide an alkaline stripped molecular complex;

(b) neutralization of the alkaline stripped molecular complex to provide a neutralized molecular complex;

(c) incubation of the neutralized molecular complex in the presence of an excess of the antigenic peptides; and

(c) slow refolding of the neutralized molecular complex in the presence of the excess of the antigenic peptides.

Appendix 2. Clean copy of all pending claims, including amendments to claims 56 and 57

28. A composition comprising a cell in which a molecular complex is bound to the surface of the cell, wherein the molecular complex comprises at least four fusion proteins, wherein:

(a) two first fusion proteins comprise an immunoglobulin heavy chain, wherein the immunoglobulin heavy chain comprises a variable region, and an extracellular portion of a first transmembrane polypeptide; and

(b) two second fusion proteins comprise an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide;

wherein the fusion proteins associate to form a molecular complex, wherein the molecular complex comprises two ligand binding sites, each ligand binding site formed by the extracellular domains of the first and second transmembrane polypeptides, wherein the affinity of the molecular complex for a cognate ligand is increased at least two-fold over a dimeric molecular complex consisting of a first and a second fusion protein.

29. The composition of claim 28 wherein the first transmembrane polypeptide is an MHC class IIβ chain and wherein the second transmembrane polypeptide is an MHC class IIα chain.

30. The composition of claim 28 wherein the first transmembrane polypeptide is a TCR α chain and wherein the second transmembrane polypeptide is a TCR β chain.

31. The composition of claim 28 further comprising a pharmaceutically acceptable carrier.

32. The composition of claim 28 wherein a population of the molecular complexes is

bound to the cell, wherein an identical antigenic peptide is bound to each ligand binding site.

51. The composition of claim 28 wherein the immunoglobulin heavy chain is an IgG1 heavy chain.

52. The composition of claim 28 wherein the immunoglobulin light chain is an Igκ chain.

53. The composition of claim 28 wherein the first fusion proteins comprise a first peptide linker between the immunoglobulin heavy chain and the extracellular domain of the first transmembrane polypeptide and wherein the second fusion proteins comprise a second peptide linker between the immunoglobulin light chain and the extracellular domain of the second transmembrane polypeptide.

54. The composition of claim 53 wherein the first peptide linker is GLY-GLY-GLY-THR-SER-GLY (SEQ ID NO:10).

55. The composition of claim 53 wherein the second peptide linker is GLY-SER-LEU-GLY-GLY-SER (SEQ ID NO:11).

56. (amended) The composition of claim 32 wherein the antigenic peptides are bound to the ligand binding sites by a method comprising the step of:

incubating the cell in the presence of the antigenic peptides, whereby the antigenic peptides are bound to the ligand binding sites.

57. (amended) The composition of claim 32 wherein the antigenic peptides are bound to the ligand binding sites by a method comprising the steps of:

(a) alkaline stripping of the molecular complex to provide an alkaline stripped molecular complex;

(b) neutralization of the alkaline stripped molecular complex to provide a neutralized molecular complex;

(c) incubation of the neutralized molecular complex in the presence of an excess of the antigenic peptides; and

(c) slow refolding of the neutralized molecular complex in the presence of the excess of the antigenic peptides.

58. The composition of claim 32 wherein the antigenic peptides are covalently bound.

59. The composition of claim 28 wherein the molecular complex is conjugated to a toxin.

60. The composition of claim 28 wherein the molecular complex is conjugated to a lymphokine or other effector molecule which stimulates an immune response.